Unexpected dimerization of 5,7-dimethyl-2-trifluoromethyl-8-azachromone induced by hydrogen sulfide

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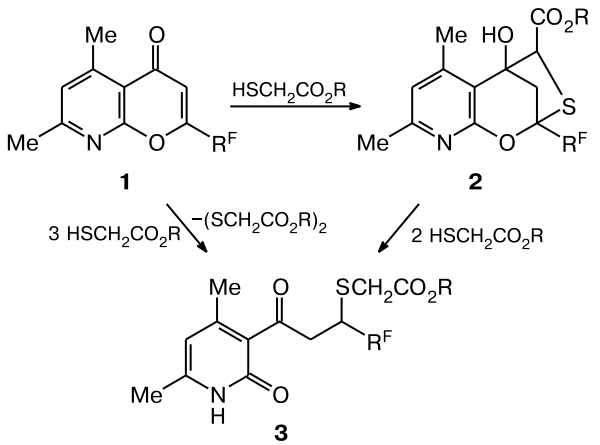
Depending on the reaction conditions, the reaction of 5,7-dimethyl-2-trifluoromethyl-8-azachromone with hydrogen sulfide afforded cyclic and linear dimers with the S—S bond. The regio- and stereochemistry of the reaction products were determined by ^{1}H and ^{13}C NMR spectroscopy.

Key words: 5,7-dimethyl-2-trifluoromethyl-8-azachromone, hydrogen sulfide, dimerization, 1,2-dithiolane, disulfides, NMR spectroscopy.

The chromone system is an important structural fragment of many biologically active compounds and it is widely used for the synthesis of various heterocyclic compounds with useful properties.[1,2] The introduction of a polyfluoroalkyl group at position 2 of chromone (2-R^F-chromones) substantially increases the activity of the pyrone ring toward nucleophiles, resulting in various new transformations, which are absolutely not typical of 2-alkylchromones.[3] It is also known that 2-polyfluoroalkyl-4*H*-pyrano[2,3-*b*]pyridin-4-one derivatives (2-R^F-8-azachromones **1**)[4] are more reactive toward amines[5] than 2-R^F-chromones, whereas the reactions of compounds **1** with 1,2-S,C-dinucleophiles, such as alkyl mercaptoacetates, occur[6,7] at the C(2) and C(4) atoms followed by the reductive cleavage of bridged system **2** to give sulfanylacetates **3** (Scheme 1).

Scheme 1



Taking into account that the C(2) atom in 2-R^F-8-azachromones **1** is highly electrophilic and these compounds can be reduced by mercaptanes, it was of interest to study the reaction of 8-azachromones **1** with hydrogen sulfide.

Results and Discussion

We found that the high-melting-point fine-crystalline product of the composition $C_{11}H_{10}F_3NO_2S$ was generated in 61% yield by bubbling hydrogen sulfide through a solution of 2-CF_3-azachromone **1a** in propan-2-ol in the presence of a catalytic amount of triethylamine (2 h, ~20 °C). The composition of this reaction product corresponds to that of thiodiketone **4a**, which is formed as a result of the attack of hydrogen sulfide on the C(2) atom followed by the cleavage of the pyrone ring. However, the ^{1}H NMR spectrum of the reaction product shows signals of two nonequivalent α-pyridone moieties (four Me groups, two aromatic protons, and two NH protons), and the ^{19}F NMR spectrum shows a singlet and a doublet ($^3J_{F,H}$ = = 9.0 Hz) of two trifluoromethyl groups, which is indicative of the dimeric nature of this compound. In addition, the ^{1}H NMR spectrum has signals of the CH_2 group (AB system, δ 3.89, $^2J_{AB}$ = 17.8 Hz), a quartet of doublets (δ 5.35), and a doublet (δ 5.89) of the methine protons with the vicinal spin-spin coupling constant ^3J = 1.6 Hz. Hence, it was concluded that the dimer has the dithiolane structure with the CH protons having the *trans* configuration (in the five-membered rings, the *cis* constant is always higher than or equal to 5 Hz).[8] In the 2D NOESY spectrum, there is a weak cross-peak between these protons, which is consistent with their vicinal arrangement

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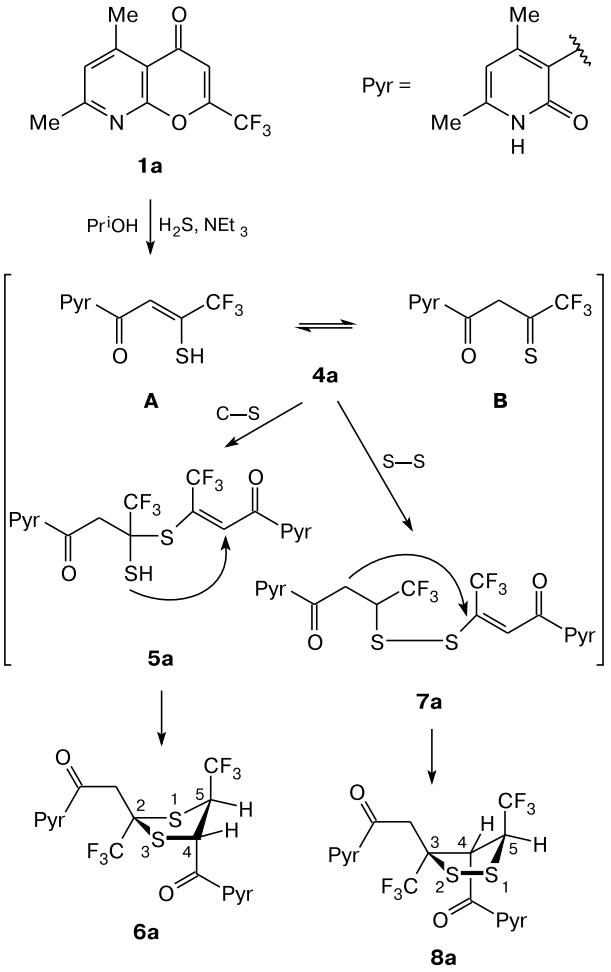
and the *trans* configuration. Taking into account that the trifluoromethyl groups are not split on each other, they are also apparently in the *trans* orientation (for the corresponding systems with the *cis*-CF_3 groups, $^6J_{F,F}$ = = 2.7—4.5 Hz,[9—11] which is indicative of their spatial proximity). In the ^{1}H-coupled ^{13}C NMR spectrum, the lowest-field signals of two carbonyl groups are most informative. These signals appear as a triplet (δ 196.3, $^2J_{C,H}$ = = 6.1 Hz) and a doublet of doublets (δ 192.9, $J_{C,H}$ = 5.1, 4.4 Hz) and are indicative of the presence of the $PyrCOCH_2$ and PyrCOCH=CH moieties in the molecule (Scheme 2).

Scheme 2



Based on the spectroscopic data, we first suggested that the dimerization of the initially formed thiodiketone **4a**, which exists in the tautomeric forms **A** and **B**, can occur through either the carbophilic (C—S) or thiophilic (S—S) addition.[12,13] In the former case, the reaction should proceed through linear dithioketal **5a**, which can undergo cyclization to 1,3-dithiolane **6a** *via* the anti-Michael addition (α-addition)[14] due to the electron-withdrawing effect of the CF_3 group. In the latter case, the cyclization of intermediate disulfide **7a** to 1,2-dithiolane **8a** can be interpreted as the standard Michael addition and, hence, seems to be more favorable (see Scheme 2).

All attempts to hydrolyze the dimeric product in an acidic medium (dilute sulfuric or hydrochloric acid), as well as in the presence of $HgCl_2$,[15] failed. This fact casts doubt on the dithioketal structure of compound **6a**. Unfortunately, the crystals of the dimer were unsuitable for the X-ray diffraction study, whereas the 2D HSQC, HMBC, and NOESY spectroscopic data did not allow the unambiguous choice between structures **6a** and **8a**. However, the comparison of the observed chemical shifts of the carbon atoms of the dithiolane ring with the corresponding values predicted by the program ACD/C+H NMR Predictors[16] provides evidence for 1,2-dithiolane structure **8a**; the chemical shifts for the first two carbon atoms of this molecule given in Table 1 are in particularly good agreement.

A change in the reaction conditions and the use of 2-CF_2H-azachromone **1b** instead of 2-CF_3-azachromone **1a** allowed us to obtain additional data consistent with the presence of the S—S bond in the cyclic dimer. It appeared that the reaction of compound **1a** with hydrogen sulfide in THF at 70 °C in the presence of triethylamine afforded a product in 93% yield whose melting point is identical to that of dithiolane **8a** but which has different spectroscopic characteristics. This compound was isolated as a mixture of diastereomers in a ratio of 7 : 3, as evidenced by the presence of two sets of signals, most of which overlap with each other. Based on the elemental analysis data and the ^{1}H NMR spectra, we assigned the structure of linear disulfide **9a** to this reaction product.

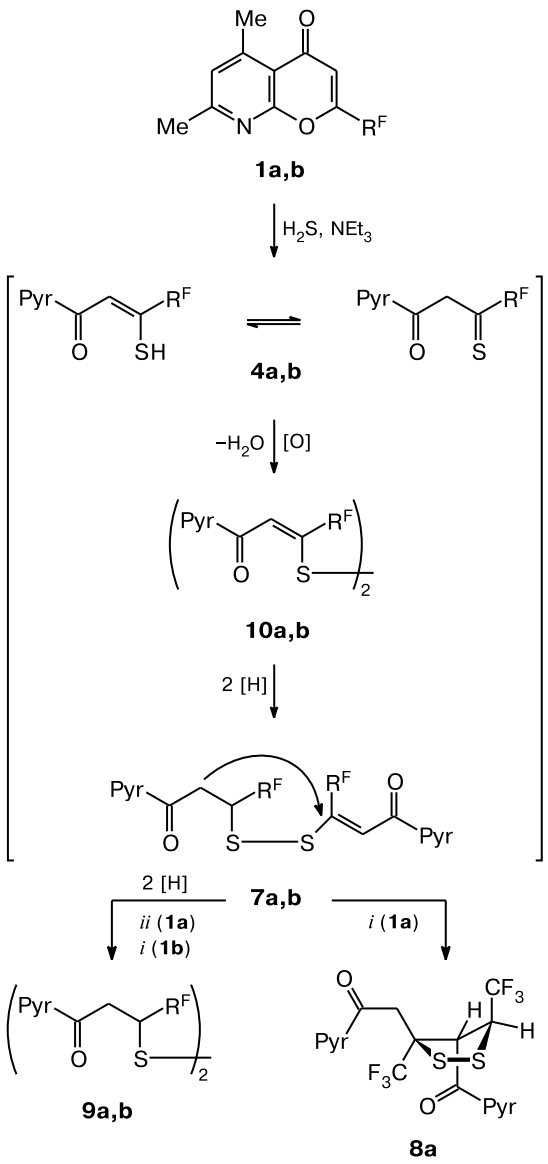
The formation of linear dimer **9a** suggests that intermediate thiodiketone **4a** undergoes the oxidative dimerization in the presence of atmospheric oxygen to form dienic dusulfide **10a**, which is reduced by hydrogen sulfide to saturated disulfide **9a** through the formation of disulfide **7a** identical to the intermediate of the thiophilic addition (see Scheme 2). Apparently, regardless of the nature of the solvent, the oxidative dimerization (**4** → **10**) characteristic of mercaptans[12,17] is the key step of the transformation under study, and partially reduced disulfide **7a** is the common intermediate, which either undergoes the Michael cyclization to 1,2-dithiolane **8a** or is reduced by H_2S to

Table 1. Comparison of the experimental ^{13}C chemical shifts (δ) of the dithiolane ring with the corresponding values predicted by the program ACD/C+H NMR Predictors[16]

C Atom	Experiment	ACD/CNMR Predictor	
		8a	**6a**
CF_3–C–CH_2	65.48 qm	66.98±10.6	73.63±12.4
PyrCO–CH	62.78 dd	61.41±10.7	57.91±6.4
CF_3–CH	51.26 dqd	58.18±8.1	56.61±7.4

linear dimer **9a**. The possible reaction pathway is presented in Scheme 3 and can serve as one of arguments in favor of structure **8a**.

Scheme 3

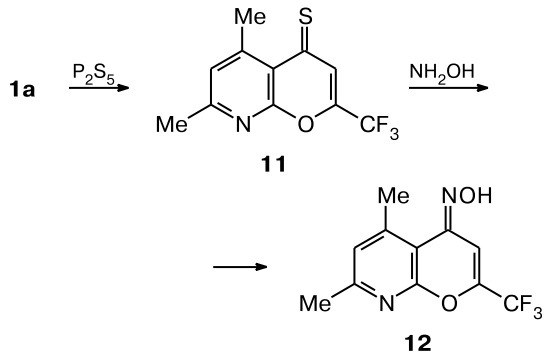


R^F = CF_3 (**a**), CF_2H (**b**)
i. Pr^iOH, ~20 °C; *ii*. THF, 70 °C.

It should be noted that under the conditions of the formation of compound **8a**, *i.e.*, in propan-2-ol at room temperature, 2-CF_2H-azachromone **1b** gives disulfide **9b** (in 82% yield) as the only reaction product existing as a mixture of two diastereomers in a ratio of 3 : 2 (^{1}H NMR spectroscopic data). Apparently, this is associated with the lower electron-withdrawing ability of the CF_2H group compared to the CF_3 group, which hinders the intramolecular cyclization by the 1,4-addition mechanism.

One of important methods for the modification of chromones is based on the synthesis of chromene-4(4*H*)-thiones, the use of which in the reactions with N-nucleophiles substantially extends the synthetic potential of the chromone system and enables the preparation of regioisomeric pyrazoles and isoxazoles.[18] Hence, we synthesized 5,7-dimethyl-2-trifluoromethyl-4*H*-pyrano[2,3-*b*]pyridine-4-thione (**11**) from azachromone **1a** and P_2S_5 by heating in toluene. Product **11** appeared to be a very unstable compound and it underwent spontaneous hydrolysis to form the starting azachromone **1a** (in 10% yield) upon storage. As expected, the reaction of thione **11** with hydroxylamine occurred at the C(4) atom to form oxime **12**. Under reflux with a drop of hydrochloric acid, oxime **12** did not undergo recyclization into the corresponding isoxazoline[18] (Scheme 4).

Scheme 4



Therefore, the reaction of 5,7-dimethyl-2-trifluoromethyl-8-azachromone (**1a**) with hydrogen sulfide affords 1,2-dithiolane **8a** or linear disulfide **9a** depending on the reaction conditions. The reaction of compound **1a** with phosphorus pentasulfide gives 4*H*-pyrano[2,3-*b*]pyridine-4-thione **11** and oxime **12**.

Experimental

The IR spectra were recorded on a Perkin—Elmer Spectrum BX-II instrument in KBr pellets. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were measured on a Bruker DRX-400 spectrometer at 400.1, 376.5, and 100.6 MHz, respectively, with the use of Me_4Si and C_6F_6 as the internal standards. The starting 8-azachromones **1a,b** were synthesized according to a known procedure.[4]

3-{2-[4-(4,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-ylcarbonyl)-3,5-bis(trifluoromethyl)-1,2-dithiolan-3-yl]acetyl}-4,6-dimethylpyridin-2(1*H*)-one (8a). Three drops of triethylamine were added to a solution of azachromone **1a** (0.2 g, 0.82 mmol) in Pr^iOH (10 mL). Hydrogen sulfide was bubbled through the reaction mixture at ~20 °C during 2 h. The precipitate that formed was filtered off, washed with boiling propan-2-ol, and dried. The yield was 0.14 g (61%), colorless powder, m.p. 238—239 °C. Found (%): C, 47.53; H, 3.58; N, 5.19. $C_{22}H_{20}F_6N_2O_4S_2$. Calculated (%): C, 47.65; H, 3.64; N, 5.05. IR, ν/cm^{-1}: 1679, 1636,

1533, 1478. ^{1}H NMR (DMSO-d_6), δ: 2.10 and 2.30 (both s, 3 H each, 2 Me); 2.18 and 2.26 (both d, 3 H each, 2 Me, J = 0.6 Hz); 3.78 (d, 1 H, C<u>H</u>H, J_{AB} = 17.8 Hz); 4.00 (d, 1 H, CH<u>H</u>, J_{AB} = = 17.8 Hz); 5.35 (qd, 1 H, H(5), $J_{H,F}$ = 9.0 Hz, J = 1.6 Hz); 5.89 (d, 1 H, H(4), J = 1.6 Hz); 6.02 and 6.18 (both s, 1 H, =CH); 12.03 and 12.26 (both s, 1 H, NH). ^{19}F NMR (DMSO-d_6, C_6F_6), δ: 91.49 (s, C(3)F_3), 93.59 (d, C(5)F_3, $J_{F,H}$ = 9.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 18.45 (qd, Me—C(4), Pyr, $^1J_{C,H}$ = 129.3 Hz, $^3J_{C,H}$ = 3.7 Hz); 18.55 (qd, Me—C(6), Pyr, $^1J_{C,H}$ = 129.2 Hz, $^3J_{C,H}$ = 4.3 Hz); 20.15 (qd, Me—C(6), Pyr, $^1J_{C,H}$ = 128.7 Hz, $^3J_{C,H}$ = 4.4 Hz); 21.18 (qd, Me—C(4), Pyr, $^1J_{C,H}$ = 129.3 Hz, $^3J_{C,H}$ = 4.8 Hz); 48.91 (t, CH_2, $^1J_{C,H}$ = 133.9 Hz); 51.26 (dqd, C(5), $^1J_{C,H}$ = 145.8 Hz, $^2J_{C,F}$ = 30.0 Hz, $^2J_{C,H}$ = 2.6 Hz); 62.78 (dd, C(4), $^1J_{C,H}$ = 141.0 Hz, $^2J_{C,H}$ = 3.9 Hz); 65.48 (q, C(3), $^2J_{C,F}$ = 29.4 Hz); 108.81 (d, C(5), Pyr, $^1J_{C,H}$ = 168.8 Hz); 110.31 (d, C(5), Pyr, $^1J_{C,H}$ = 168.8 Hz); 118.90 (m, C(3), Pyr); 122.98 (qdd, C(3), Pyr, $^3J_{C,H}$ = 4.5 Hz, $^3J_{C,H}$ = 3.9 Hz, $^3J_{C,H}$ = 0.8 Hz); 125.89 (q, C(3)—<u>C</u>F_3, $^1J_{C,F}$ = 278.1 Hz); 126.01 (q, C(5)—<u>C</u>F_3, $^1J_{C,F}$ = 281.3 Hz); 149.07 (qd, C(6), Pyr, $^2J_{C,Me}$ = 6.2 Hz, $^2J_{C,H}$ = = 4.1 Hz); 150.59 (qd, C(6), Pyr, $^2J_{C,Me}$ = 6.2 Hz, $^2J_{C,H}$ = 3.9 Hz); 154.81 (qd, C(4), Pyr, $^2J_{C,Me}$ = 5.7 Hz, $^2J_{C,H}$ = 1.2 Hz); 159.35 (qd, C(4), Pyr, $^2J_{C,Me}$ = 6.2 Hz, $^2J_{C,H}$ = 1.5 Hz); 161.68 (s, NC=O); 162.47 (s, NC=O); 192.92 (dd, C(4)—C=O, $^2J_{C,H}$ = 5.1 Hz, $^3J_{C,H}$ = 4.4 Hz); 196.31 (t, CH_2—C=O, $^2J_{C,H}$ = = 6.1 Hz).

Bis[1-trifluoromethyl-3-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxopropyl] disulfide (9a). Three drops of triethylamine were added to a solution of azachromone **1a** (250 mg, 0.10 mmol) in anhydrous THF (5 mL). Dry H_2S was bubbled through the reaction mixture under reflux during 1.5 h. Then the solution was concentrated, and the fine-crystalline precipitate that formed was washed with boiling Pr^{i}OH and diethyl ether, and dried. The yield was 320 mg (93%), a mixture of two diastereomers (7 : 3), colorless powder, m.p. 237—240 °C. Found (%): C, 47.17; H, 3.79; N, 4.80. $C_{22}H_{22}F_6N_2O_4S_2$. Calculated (%): C, 47.48; H, 3.98; N, 5.03. IR, ν/cm^{-1}: 1679, 1644, 1619, 1534, 1478. ^{1}H NMR (DMSO-d_6), δ: 2.17 and 2.18 (both s, 3 H each, 2 Me); 3.27—3.51 (m, 1 H, C<u>H</u>H); 3.58—3,67 (m, 1 H, CH<u>H</u>); 4.12—4.18 (m, 0.3 H, CH); 4.29—4.34 (m, 0.7 H, CH); 6.02 (m, 0.7 H, =CH); 6.04 (m, 0.3 H, =CH); 12.02 (s, 1 H, NH).

Bis[1-difluoromethyl-3-(4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)-3-oxopropyl] disulfide (9b) was synthesized as a mixture of two diastereomers (3 : 2) under the conditions described above for 1,2-dithiolane **8a**. The yield was 82%, colorless powder, m.p. 205—208 °C. Found (%): C, 50.51; H, 4.35; N, 5.05. $C_{22}H_{24}F_4N_2O_4S_2$. Calculated (%): C, 50.76; H, 4.65; N, 5.38. ^{1}H NMR, δ: 2.14 and 2.17 (both s, 3 H each, 2 Me); 3.20—3.50 (m, 2 H, CH_2); 3.60—3.80 (m, 0.6 H, CH); 3.85—3.95 (m, 0.4 H, CH); 6.00 (s, 0.6 H, =CH); 6.01 (s, 0.4 H, =CH); 6.27 (t, 1 H, CF_2H, $^2J_{H,F}$ = 56.2 Hz), 11.98 (s, 1 H, NH).

5,7-Dimethyl-2-trifluoromethyl-4*H*-pyrano[2,3-*b*]pyridine-4-thione (11). A mixture of azachromone **1a** (1.1 g, 4.5 mmol) and P_2S_5 (1.0 g, 4.5 mmol) in dry toluene (5 mL) was refluxed with stirring for 4 h. The cooled reaction mixture was filtered, the solvent was evaporated from the filtrate, and the residue was recrystallized from hexane after the passing of the hot solution through 2 cm^3 of silica gel. The yield was 0.96 g (82%), dark green needle-like crystals, m.p. 58—60 °C. Found (%): C, 50.68; H, 3.08; N, 5.37. $C_{11}H_8F_3NOS$. Calculated (%): C, 50.96; H, 3.11; N, 5.40. IR, ν/cm^{-1}: 1656, 1596, 1527. ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 3 H, Me(7)); 2.93 (s, 3 H, Me(5)); 7.14 (s, 1 H, H(6)); 7.34 (s, 1 H, H(3)).

5,7-Dimethyl-2-trifluoromethyl-4*H*-pyrano[2,3-*b*]pyridin-4-one oxime (12). Azachromonethione **11** (0.25 g, 1 mmol) was added to a solution of hydroxylamine in Pr^{i}OH (3 mL), which was prepared from hydroxylamine hydrochloride (0.26 g, 3.8 mmol) and KOH (0.2 g, 3.6 mmol). The reaction mixture was stirred at ~20 °C for 20 min (the reaction was accompanied by the vigorous evolution of H_2S). Then the reaction mixture was diluted with water (10 mL). The precipitate was filtered off, washed with water, dried, and recrystallized from toluene. The yield was 0.08 g (30%), colorless crystals, m.p. 239—240 °C. Found (%): C, 50.97; H, 3.24; N, 10.57. $C_{11}H_9F_3N_2O_2$. Calculated (%): C, 51.17; H, 3.51; N, 10.85. IR, ν/cm^{-1}: 3233, 1678, 1611, 1596, 1547. ^{1}H NMR (DMSO-d_6), δ: 2.42 (s, 3 H, Me(7)); 2.59 (s, 3 H, Me(5)); 7.18 (s, 2 H, H(3), H(6)); 11.82 (s, 1 H, OH).

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